

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Alfaxan Multidose 10 mg/ml solution for injection for dogs and cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0591/001 (formerly UK/V/0684/001)
Name, strength and pharmaceutical form	Alfaxan Multidose 10 mg/ml solution for injection for dogs and cats
Active substances(s)	Alfaxalone
Applicant	Jurox (Ireland) Limited The Black Church St Mary's Place D07 P4AX Ireland
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Date of Authorisation	19 December 2018 (UK) 07 January 2019 (IE)
Target species	Cats,Dogs
Indication for use	As an induction agent prior to inhalation anaesthesia. As a sole anaesthetic agent for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures.
ATCvet code	QN01AX05
Concerned Member States	Austria, Czech Republic, Denmark, Germany, Ireland (now RMS), Norway, Poland, Portugal, Slovakia, Spain.

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Alfaxan Multidose 10 mg/ml Solution for Injection for Dogs and Cats, submitted under Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference product is Alfaxan 10 mg/ml Solution for Injection for Dogs and Cats, marketed in the UK since November 2006. The product is indicated for the induction and maintenance of anaesthesia for the performance of examination or surgical procedures.

The induction dose for successful anaesthesia is based on data taken from laboratory and field studies and is appropriate for 9 out of 10 patients:

	DOGS		CATS	
	Un-premedicated	Premedicated	Un-premedicated	Premedicated
mg/kg	3	2	5	5
ml/kg	0.3	0.2	0.5	0.5

Further information on induction and maintenance of anaesthesia is available in the Summary of Product Characteristics (SPC), which should be referred to when using the product.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended.

Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition

The product contains 10 mg/ml alfaxalone and the excipients hydroxypropylbetadex, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, chlorocresol, benzethonium chloride, ethanol, sodium hydroxide (for pH adjustment), hydrochloric acid, concentrated (for pH adjustment) and water for injections.

The container/closure system consists of a cardboard box with one glass vial of 10 ml or 20 ml with a bromobutyl rubber stopper and aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the mixing and dissolving of the ingredients at various temperatures, adjustment to target weight where appropriate, cooling, filtering and filling into sterilised vials. A quality control analysis is then performed against the complete release specification.

II.C. Control of Starting Materials

The active substance is alfaxalone, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. Appropriate certificates of suitability were presented.

In-house specifications in accordance with the requirement of the Ph. Eur were provided for all excipients and immediate packaging.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: appearance, clarity, density, identity of active substance and key elements, pH, degradation products, sterility and the confirmed absence of bacterial endotoxins.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 28 days.

Store below 25°C.

Keep the container in the outer carton in order to protect from light.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

The applicant has submitted a user risk assessment (URA) and an environmental risk assessment (ERA). No other pharmacological or toxicological data are required for this generic application. The applicant has claimed an exemption from the requirement to demonstrate bioequivalence.

Pharmacodynamic properties

Alfaxalone (3- α -hydroxy-5- α -pregnane-11,20-dione) is a neuroactive steroid molecule with properties of a general anaesthetic. The primary mechanism for the anaesthetic action of alfaxalone is modulation of neuronal cell membrane chloride ion transport, induced by binding of alfaxalone to GABAA cell surface receptors.

Pharmacokinetic particulars

In cats following a single intravenous dose of alfaxalone at 5 mg/kg bw, the mean plasma elimination half-life (t_{1/2}) is approximately 45 minutes. Plasma clearance is 25 ml/kg/min. Volume of distribution is 1.8 L/kg.

In dogs following a single intravenous dose of alfaxalone at 2 mg/kg bw, the mean plasma elimination half-life (t_{1/2}) is approximately 25 minutes. Plasma clearance is 59 ml/kg/min. Volume of distribution is 2.4 L/kg.

In both dogs and cats the elimination of alfaxalone demonstrates non-linear (dose-dependent) pharmacokinetics.

In vitro cat and dog hepatocyte studies show that alfaxalone experiences both Phase I (cytochrome P450 dependent) and Phase II (conjugation dependent) metabolism. Both cats and dogs form the same five (5) Phase I alfaxalone metabolites. The Phase II metabolites observed in cats are alfaxalone sulphate and alfaxalone glucuronide, while alfaxalone glucuronide is observed in the dog.

Alfaxalone metabolites are likely to be eliminated from the dog and cat by the hepatic/faecal and renal routes, similar to other species.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The user warnings were updated from that of the reference product. Therefore the following applicant's user recommendations are appropriate:

- This product is a sedative, exercise caution to avoid accidental self-injection.
- Preferably use a guarded needle until the moment of injection.
- In case of accidental self-injection seek immediate medical attention and show the product literature.
- The product may cause irritation if it comes into contact with the skin or eyes.
- Rinse any splashes from skin or eyes immediately with water.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low, and is not expected to pose a risk when used as recommended. A Phase II ERA was not required.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

The studies submitted with this application were previously assessed during an application for Alfaxan Multidose 10 mg/ml Solution for Injection for Dogs, Cats and Pet Rabbits, authorised in the UK since February 2018.

The pharmacodynamic and pharmacokinetic properties of the proposed product are the same as those of the reference product. Due to the nature of the application, there was no necessity to submit the results of pre-clinical trials for pharmacodynamics properties.

Two bioequivalence studies were provided to establish bioequivalence between the proposed and reference product, one in dogs and one in cats.

The first study, in dogs, was a randomised, two-period, cross-over study design with a seven day washout period between treatments. Twenty-four healthy animals were included in the study; two were excluded during the study for health reasons. Animals were maintained under controlled conditions, with food withdrawn 10 hours prior to either treatment. Each treatment group was divided into 2 cohorts of 6 animals each, and were dosed at appropriate time-points. Dogs were dosed with the proposed or reference product at 3 mg alfaxalone/kg bodyweight intravenously in anaesthetised animals, and blood samples

were taken before and after treatment. The animals were monitored for safety and efficacy variables. After a 7 day washout period, the alternative product was administered.

Pharmacokinetic parameters measured were C_{max} [1], T_{max} [2], AUC_{0-t} [3] and AUC_{0-inf} [4].

Pivotal pharmacokinetic parameters measured were AUC_{0-tr} (as AUC_{last} [5]), and C_{max} . Suitable statistical analyses were performed on all results, as appropriate.

90% confidence limits for AUC_{0-t} and C_{max} for the proposed and reference products fell within the pre-accepted bounds of 80-125%, thereby demonstrating bioequivalence.

The second study, in cats, was a randomised, two-period, cross-over study design with a seven day washout period between treatments. Twenty-four healthy animals were included in the study, four were excluded during the study, 2 animals were fractious and 2 were excluded for weight reasons. Animals were maintained under controlled conditions, with food withdrawn 10 hours prior to either treatment. Each treatment group was divided into 2 cohorts of 6 animals each, and were dosed at appropriate time-points. Dogs were dosed with the proposed or reference product at 5 mg alfaxalone/kg bodyweight intravenously in anaesthetised animals, and blood samples were taken before and after treatment. The animals were monitored for safety and efficacy variables. After a 7 day washout period, the alternative product was administered.

Pharmacokinetic parameters measured were C_{max} , T_{max} , AUC_{0-t} and AUC_{0-inf} .

Pivotal pharmacokinetic parameters measured were AUC_{0-tr} (as AUC_{last}), and C_{max} . Suitable statistical analyses were performed on all results, as appropriate.

90% confidence limits for AUC_{0-t} and C_{max} for the proposed and reference products fell within the pre-accepted bounds of 80-125%, thereby demonstrating bioequivalence.

Suitable 'proof of principle' studies were presented, which assured the safety of the preservative system, not present in the reference product. Validation of data relating to the analytical method for the quantification of alfaxalone in cat/dog plasma were also submitted.

Tolerance in the Target Species

No data were required for this section other than the proof of principle studies which supported the use of the excipients.

IV.II. Clinical Documentation

Due to the nature of the application, no data were required for this section.

[1] C_{max} - Maximum concentration of active substance in the blood plasma.

[2] T_{max} - Time at which maximum concentration of the active substance was observed.

[3] AUC_{0-t} - Area under the curve over specified time points.

[4] AUC_{0-inf} - Area under the curve from time 0 to infinity.

[5] AUC_{0-last} Area under the curve from 0 to last time point.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.